# Facile synthesis of planar chiral *N*-oxides and their use in Lewis base catalysis†‡§

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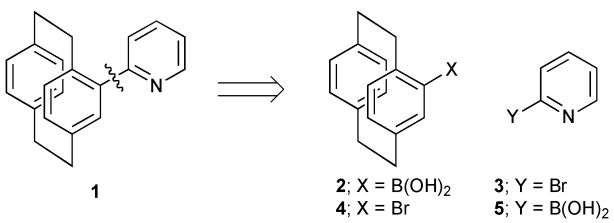
**A rapid and versatile method for the preparation of planar chiral [2.2]paracyclophane-derived pyridines and pyridine *N*-oxides is reported. The potential utility of these compounds in Lewis base catalysis is briefly introduced.**



Chiral heteroaromatics are a valuable motif in enantioselective catalysis and related disciplines.[1–4] Planar chiral heterocycles are uncommon, with the majority based on ferrocene or related complexes. Chiral cyclophane-based heteroaromatics is a field ripe for exploration.[4–8] We are interested in the synthesis of planar chiral [2.2]paracyclophane derivatives[9] and in this communication, we disclose a rapid route to planar chiral pyridine *N*-oxides and reveal their potential as Lewis base catalysts.

A multitude of [2.2]paracyclophane-derived heterocycles have been reported, but have found little utility as the syntheses are either convoluted or of limited generality.[5] To overcome this limitation, we sought a versatile route to rapidly prepare 2-([2.2]paracyclophan-4-yl)pyridines **1** (Scheme 1). Pyridines and pyridine *N*-oxides have an excellent pedigree as ligands for catalysis, photoelectronic dyes and metal–organic frameworks as well as being common organocatalyst.[1,2,10,11] 2-([2.2]Paracyclophan-4-yl)pyridines and related compounds are known; Hopf has reported a simple route to a pyridinyl-[2.2]paracyclophane by a nitrone cycloaddition, but the generality of this reaction has not been assessed,[12] whilst Pfaltz *et al.*[6] and Andrus *et al.*[8] have accessed derivatives of [2](1,4)benzeno[2](2,5)pyridinophane in generally low yields.




**Scheme 1** Possible syntheses of 2-([2.2]paracyclophane-4-yl)-pyridines.

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† Dedicated to the memory of Keith Fagnou.

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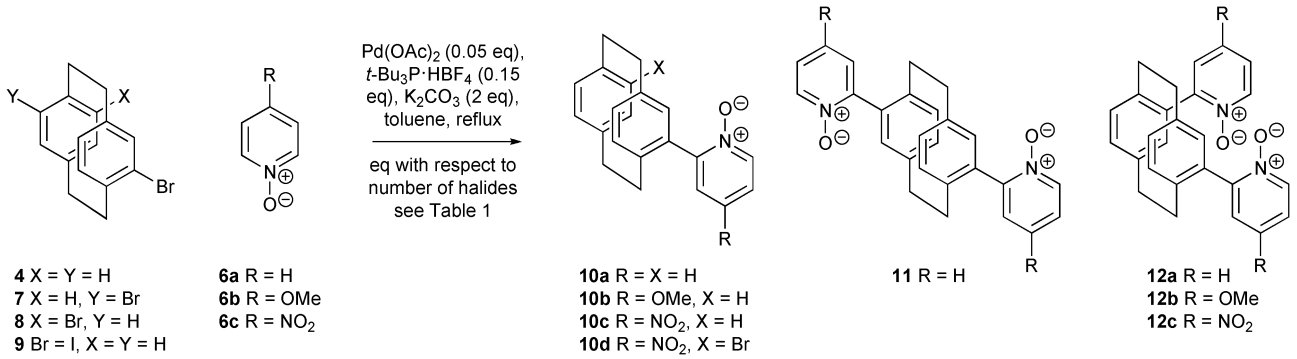
The simplest route to 2-([2.2]paracyclophan-4-yl)pyridines **1** involves the cross coupling of suitably functionalised [2.2]paracyclophane derivative **2** or **4** with its complementary 2-pyridinyl unit **3** or **5** (Scheme 1); frustratingly, such chemistry is problematic. Whilst 2-halopyridines **3** readily participate in the cross coupling reactions, the corresponding 4-[2.2]paracyclophanyl boronic acids **2** are unstable.[13] Reversing the functionality fails to overcome this problem; 4-halo[2.2]paracyclophanes **4** are suitable precursors but 2-pyridyl boronic acids **5** are inherently unstable and rarely employed in cross-coupling reactions. The direct arylation chemistry of Fagnou *et al.* appeared to offer an effective solution to these limitations, permitting the coupling of 4-halo[2.2]paracyclophanes **4** and pyridine *N*-oxides **6**.[14–16]

To evaluate the utility of this methodology in [2.2]para-cyclophane chemistry, racemic 4-bromo[2.2]paracyclophane **4** and pyridine *N*-oxide **6a** were treated with tri-*tert*-butyl-phosphonium tetrafluoroborate, palladium(II) acetate and potassium carbonate at reflux in toluene (Scheme 2; Table 1; Entry 1).§ The desired **10a** was isolated in 66% yield with the remainder of the material comprising of [2.2]paracyclophane, the product of proto-debromination. A perfunctory attempt was made to optimise the reaction but the only improvement was obtained by increasing the catalyst loading. Use of the more reactive 4-iodo[2.2]paracyclophane with the addition of $Ag_2CO_3$ led to a slight improvement (Entry 4) but this did not offset the additional steps required to form the iodide from the bromide. Reducing the amount of pyridine *N*-oxide to less than 3 eq. results in a dramatic decrease in yield. The reaction appears general, with both the electron rich 4-methoxypyridine *N*-oxide **6b** and the electron deficient 4-nitropyridine *N*-oxide **6c** undergoing coupling in respectable yields (Entries 5 and 6). The initial attempt to form a bis(pyridine *N*-oxide) utilised pseudo-*para* 4,16-dibromo[2.2]paracyclophane **7**, thus minimising any inter-deck interactions. As expected a mixture of the desired bis(pyridine *N*-oxide) **11** and debromo mono(pyridine *N*-oxide) **10a** was formed (Entry 7). More rewarding was the successful coupling of the pseudo-*ortho* 4,12-dibromo[2.2]-paracyclophane derivative **12**. Under our standard reaction conditions, all three pyridine *N*-oxides, **6a**, **6b** and **6c**, reacted to give mixtures of mono- and bis(pyridine *N*-oxides) (Entries 8, 9 and 10). Generally, the combined yields are excellent. It is unclear if the variation in ratio of mono- to bis(pyridine *N*-oxide) is due to steric hindrance or an electronic effect affecting the rate of proto-debromination. Interestingly, only in the reaction of more reactive nitro derivative[16] was the bromo pyridine *N*-oxide observed (Entry 10). The optimum yield of the bis(pyridine *N*-oxide) **11**/**12** was obtained by doubling the number of equivalents of all reagents. Currently, the major limitation to this methodology is associated with




**Scheme 2** Synthesis of mono- and bis(pyridine *N*-oxides). See Table 1 for yields.

**Table 1** Synthesis of [2.2]paracyclophane-based pyridine *N*-oxides

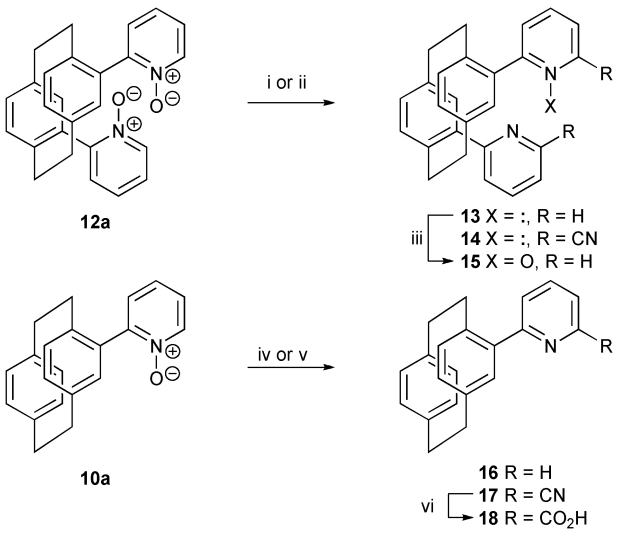
| Entry | Halide | R | Product(s) (yield %) | |
|---|---|---|---|---|
| 1 | **4** | H | 66 (**10a**) | |
| 2[a] | **4** | H | 41 (**10a**) | |
| 3[b] | **4** | H | 74 (**10a**) | |
| 4[c] | **9** | H | 65 (**10a**) | |
| 5 | **4** | OMe | 62 (**10b**) | |
| 6 | **4** | $NO_2$ | 59 (**10c**) | |
| 7 | **7** | H | 38 (**10a**) | 38 (**11**) |
| 8 | (*R*)-**8** | H | 29 ((*R*)-**10a**) | 54 ((*R*)-**12a**) |
| 9 | (*R*)-**8** | OMe | 53 ((*R*)-**10b**) | 32 ((*R*)-**12b**) |
| 10 | (±)-**8** | $NO_2$ | 32 ((±)-**10c**), 15 ((±)-**10d**) | 25 ((±)-**12c**) |

[a] Reaction employed $Cy_3P{\cdot}HBF_4$ as ligand. [b] Reaction employed 8 eq. **6a**, 0.1 eq. $Pd(OAc)_2$, 0.3 eq. *t*-$Bu_3P{\cdot}HBF_4$ and 8.0 eq. $K_2CO_3$. [c] 3.0 eq. **6a**, 0.05 eq. $Pd(OAc)_2$, 0.15 eq. *t*-$Bu_3P{\cdot}HBF_4$, 0.5 eq. $Ag_2CO_3$, 2.0 eq. $K_2CO_3$.

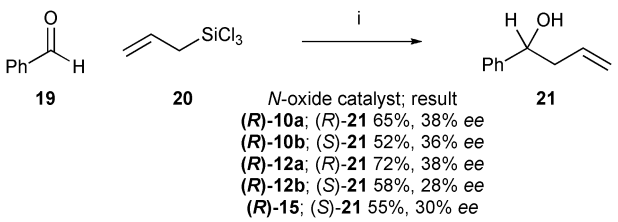
purification; all the products and by-products display limited solubility precluding simple chromatography or recrystallisation techniques. Purification withstanding, this chemistry is extremely practicable; it requires no special precautions, such as inert atmosphere, and permits the coupling of aryl bromides and pyridine *N*-oxides simply by heating in the presence of palladium(II) acetate and an air-stable phosphine salt.

The mono- and bis(pyridine *N*-oxides) are readily modified to form various pyridines. Simple reduction of **10a** and **12a** is best achieved by treatment with trichlorosilane and triethylamine, although other methods also furnish the products (Scheme 3).[15,16] The dipyridine **13** can be selectively oxidised to the mixed pyridine/*N*-oxide–pyridine **15** by reaction with *m*CPBA. The *N*-oxide functionality permits functionalisation of C6 of the pyridine moiety. Treatment of either **10a** or **12a** with diethylcarbamoyl chloride and trimethylsilyl cyanide[17] results in the formation of the nitriles **17** and **14** in moderate yield. Simple acid hydrolysis furnishes potentially valuable chiral pyridine-2-carboxylic acids such as **18** (Scheme 3). Curiously, addition of the nitrile moiety to **11** has proven impossible under these conditions.

The utility of these novel *N*-oxides was demonstrated in the Lewis base-mediated allylation of benzaldehyde with allyltrichlorosilane.[1,11,18,19] Enantiomerically pure mono- and bis(pyridine *N*-oxides) (*R*)-**10a**,**b**, (*R*)-**12a**,**b** and (*R*)-**15** were prepared from (*R*)-4,12-dibromo[2.2]paracyclophane. For these preliminary tests, benzaldehyde **19** was treated with allyltrichlorosilane **20**, diisopropylethylamine and 10 mol% *N*-oxide in $CH_2Cl_2$ at −78 °C (Scheme 4); no attempt was made to optimise the conditions. All the *N*-oxides tested displayed high activity and whilst only modest enantioselectivities were observed, the results exhibit an intriguing electronic effect. Both the mono- and bis-unsubstituted pyridine *N*-oxides (*R*)-**10a** and (*R*)-**12a** gave homoallylic alcohol (*R*)-**21** with identical enantioselectivities (38% ee). The electron rich, methoxy substituted pyridine *N*-oxides (*R*)-**10b** and (*R*)-**12b** furnished the opposite enantiomer, (*S*)-**21**, with comparable enantioselectivity (36% ee and 28% ee, respectively).




**Scheme 3** *Reagents and conditions*: (i) $Cl_3SiH$ (15 eq.), $Et_3N$ (10 eq.), $CH_2Cl_2$, reflux (**13**, 88%); (ii) TMSCN (2 × 3 eq.), diethylcarbamoyl chloride (2 × 3 eq.), $CH_2Cl_2$, rt (**14**, 51%); (iii) *m*CPBA (1.1 eq.), $CH_2Cl_2$, rt (**15**, 65%); (iv) $Cl_3SiH$ (15 eq.), $Et_3N$ (10 eq.), $CH_2Cl_2$, reflux (**16**, 80%); (v) TMSCN (2 × 3 eq.), diethylcarbamoyl chloride (2 × 3 eq.), $CH_2Cl_2$, rt (**17**, 60%); (vi) 6 M HCl, reflux (**18**, 93%).




**Scheme 4** *Reagents and conditions*: (i) *N*-oxide (*R*)-**10a**, **10b**, **12a**, **12b** or **15** (0.1 eq.), $iPr_2NEt$, $CH_2Cl_2$, −78 °C.



Most interestingly, the unsubstituted mixed pyridine/pyridine *N*-oxide **15** gave the opposite result compared to unsubstituted **12a** providing (*S*)-**21** with 30% ee. Simple steric factors do not explain these differences and we surmise that electronic factors play a crucial role.[19] It is unlikely that either of the bis(pyridine *N*-oxides) are bidentate as they give the same enantioselectivity as their monodentate counterparts.

In conclusion, we have outlined a new strategy for the preparation of planar chiral pyridines and pyridine *N*-oxides. The route is based on Fagnou's direct arylation methodology and permits the synthesis of these potentially valuable compounds in just two steps from [2.2]paracyclophane. These compounds can be considered our first generation of paracyclophane-based planar chiral Lewis base catalysts. Further studies will be directed at delineating the electronic effects in the allylation reaction and modifying the basic framework to form better Lewis base catalysts. The use of these compounds in other applications, such as palladacycle formation, will also be investigated and disclosed in due course.

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